Chapter I

INTRODUCTION
1.1. Introduction

The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms [1]. Development of a successful oral controlled release formulation requires an understanding of three aspects: (a) gastrointestinal physiology (b) physiochemical properties of the drug and (c) dosage form characteristics [2]. In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time [1]. Using controlled release technology, oral delivery for 24 h (hours) is possible for many drugs; however, the substance must be well absorbed throughout the whole gastrointestinal tract. A significant obstacle may arise if there is a narrow window for drug absorption in the gastrointestinal tract (GIT), if a stability problem exists in gastrointestinal fluids, or the drug is poorly soluble in the intestine or acts locally in the stomach. Thus, the real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of the drugs for more than 12 h, but to prolong the presence of the dosage forms in the stomach or somewhere in the upper intestine until the entire drug is released over the desired period of time [3]. These considerations have led to the development of a unique oral controlled release dosage form with gastroretentive properties. Floating Drug Delivery System (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This result in a better control of the fluctuations in plasma drug concentration and improves bioavailability, therapeutic efficacy and may even also allow a possible reduction in the dose because of steady therapeutic levels of different antimicrobials.
The reduction in fluctuations in therapeutic levels minimizes the risk of resistance especially in case of β-lactam antibiotics (penicillin’s and cephalosporins) [4]. Gastroretentive floating dosage forms are also useful for local as well as sustained delivery of antimicrobials to treat *Helicobacter pylori* (*H. pylori*) infection which is the cause of peptic ulcers. In this project oil entrapped chitosan coated amoxicillin trihydrate floating beads were prepared by the emulsion gelation method and were evaluated for various parameters like size, weight variation, drug entrapment efficiency, in-vitro floating, in-vitro drug release, in-vitro *H. pylori* growth inhibition and in-vivo floating with the aim to localize the antibiotic at the site of *H. pylori* infection to achieve higher bactericidal concentration and thereby to improve the therapeutic efficacy of the drug.

### 1.2. Floating Drug Delivery System

Floating systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time (Fig:1.1).

![Fig. 1.1. Floating systems: Low-density floating dosage (A) and the density of dosage can be lowered after administration (B).](image-url)
1.3. Advantages of Floating Drug Delivery System

➤ **Predictable drug release from dosage forms:** Majority of drugs are preferentially absorbed from the upper part of the small intestine. Floating drug delivery system has the advantage that after oral administration; dosage form would be retained in the stomach and releases the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper GIT.

➤ **Pharmacokinetic advantages:** As sustained release systems, floating dosage forms offer various potential advantages evident from several recent publications. Drugs that have poor bioavailability because their absorption is restricted to the upper GIT can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability. e.g. Furosemide [5].

➤ **Reduces the gastric irritation:** Floating drug delivery is useful to reduce the gastric irritation caused by various non steroidal anti-inflammatory drugs.

➤ **Pharmacotherapy of the stomach:** Gastroretentive floating drug delivery greatly improves the pharmacotherapy of the stomach through local drug release resulting in high drug concentrations at the gastric mucosa [6]. e.g. Eradication of *H. pylori*, the causative agent of chronic dyspepsia, gastric and duodenal ulcer by Clarithromycin [7], Amoxicillin [8] etc.

➤ **Minimized adverse activity at the colon:** Retention of the drug in the stomach minimizes the amount of drug that reaches the colon. This pharmacodynamic aspect provides the rationale for gastroretentive formulations of beta-lactam antibiotics (penicillins and cephalosporins) [4] that are absorbed only from the small intestine and whose presence in the colon leads to the development of microorganism’s resistance.
➢ **Absorption Enhancement**: A floating dosage form is feasible approach especially for drugs which have limited absorption site in stomach and upper small intestine. e.g. Frusemide [9], P-amino benzoic acid [10] etc.

➢ **Enhanced bioavailability**: There are some drugs such as Ofloxacin [11], Chlordiazepoxide, Diazepam, and Cinnarizine [12] etc which are poorly soluble at intestinal pH and dissolution is the rate limiting step in the absorption and bioavailability. Floating drug delivery of these drugs increases their bioavailability by reducing their wastage.

➢ **Enhanced first pass biotransformation**: In similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner by FDDS, rather than by a bolus input.

➢ **Reduce fluctuation of drug concentration**: Continuous input of the drug following control release gastro retentive dosage form (GRDF) administration produces blood drug concentration within a narrower range compared to the immediate release dosage forms. Thus, fluctuation in drug effects is minimized and concentration dependent adverse effects that are associated with peak concentration can be prevented. This feature is of special importance for drugs with a narrow therapeutic index. [13]

➢ **Improved selectivity in receptor activation**: Minimization of fluctuation in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drug that activates different type of receptors at different concentration.
1.4. Disadvantages of Floating Drug Delivery System

- There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
- Drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
- Furthermore, some drugs, such as Isosorbide dinitrate, that are absorbed equally well throughout the GIT will not benefit from incorporation into a gastric retention system.

1.5. Mechanism of Floating Systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (Fig.1.2.), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This resulted in an increased gastric retention time (GRT) and a better control of the fluctuations of plasma drug concentration.
Fig. 1.2. Mechanism of floating system, GF= Gastric fluid.

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Fig. 1.2). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations [14].

\[ F = F_{buoyancy} - F_{gravity} = (D_f - D_s) \cdot g \cdot v \]

Where, \( F = \) total vertical force, \( D_f = \) fluid density, \( D_s = \) object density, \( v = \) volume and \( g = \) acceleration due to gravity.
1.6. Basic Gastrointestinal Tract Physiology

The GIT is essentially a tube about nine metres long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The stomach is an organ with a capacity for storage and mixing [15]. Anatomically (Fig.1.3.) the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as reservoir for undigested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling action.

![Anatomy of human stomach.](image)

Gastric emptying occurs during fasting as well as in fed states (Fig. 1.4). The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 h [16]. This is
called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases (Fig. 1.5) as described by Wilson and Washington [17].

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate [16].
Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate. The concentration of the hormone motilin in the blood controls the duration of the phases [18].

Fig. 1.5. Diagram showing the four phases of migrating myoelectric cycle.

1.7. Factors Controlling Gastric Retention of Dosage Forms

The floating time of dosage forms is controlled by several factors such as

➢ **Density of dosage form:** Density of the dosage form must be lower than the gastric fluids for showing the floating behavior. Normally a density of <1.0 gm/cm³ is required to exhibit floating property.

➢ **Size of dosage form:** Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT.
Shape of dosage form: It was reported that tetrahedron and ring shaped devices have a better gastric residence time as compared with other shapes.

Fed or unfed state: Under fasting conditions, the gastrointestinal motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 2 to 3 h [19]. The MMC sweeps undigested materials from the stomach and if the timing of the formulation coincides with that of the MMC, the gastroretentive time of the dosage form can be expected to be very short. However, in the fed state, MMC is delayed resulting in slowdown of gastric emptying rate [16].

Nature of meal: Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.[20]

Caloric content and frequency of feed: GRT can be increased with a meal that is high in proteins and fats and when successive meals are given compared with a single meal due to the low frequency of MMC.

Biological factors: Biological factors such as age, body mass index, gender, posture, and diseased states (diabetes, Chron’s disease) influence gastric emptying. In the case of elderly persons, especially those over 70, have a significantly longer GRT. Mean ambulatory GRT in males is less compared with their age and race-matched female counterparts, regardless of the weight, height and body surface. Generally females have slower gastric emptying rates than males. GRT also can vary between supine and upright ambulatory states of the patient [21]. Stress increases gastric emptying rates while depression slows it down [22].

Intake of drugs: Anti-cholinergic and opiates increase the GRT [23] by decreasing the peristalsis where as prokinetics like Metoclopramide decrease the GRT by increasing peristalsis.
1.8. Suitable Drug Candidates for Floating Dosage Forms

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3 h [24].

In general, appropriate candidates for floating drug delivery are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Narrow absorption window in GIT, e.g., Riboflavin and Levodopa.
- Primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, Chlordiazepoxide and Cinnarazine.
- Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- Low density form of the dosage forms that causes buoyancy in gastric fluid [25]
- High density dosage forms which are retained in the bottom of the stomach [26]
- Bioadhesion to stomach mucosa [27].
- Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients [28].
Expansion by swelling or unfolding to a large size which limits emptying of the dosage form through the pyloric sphincter [29].

Table 1.1. Commonly used drugs in different type of floating dosage forms:

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>Acetaminophen, Ampicillin, Amoxicillin trihydrate, Ciprofloxacin, Levofloxacin, Atenolol, Diltiazem.</td>
</tr>
<tr>
<td>Capsules</td>
<td>Clarithromycin, Celecoxib, Diazepam, Furosemide,</td>
</tr>
<tr>
<td>Beads</td>
<td>Amoxicillin, Clarithromycin, Ciprofloxacin, Levofloxacin hemihydrate.</td>
</tr>
<tr>
<td>Granules</td>
<td>Diclofenac sodium, Êindomethacin, Gatifloxacin.</td>
</tr>
<tr>
<td>Microspheres</td>
<td>Amoxicillin, Cefopodoxim proxetil, Ciprofloxacin, Clarithromycin, Ofloxacin, Aspirin, Griseofulvin.</td>
</tr>
<tr>
<td>Nanoparticles</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>In Situ Gel</td>
<td>Levofloxacin hemihydrate.</td>
</tr>
</tbody>
</table>

Table 1.2. Available marketed gastroretentive formulations:

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Drug (dose)</th>
<th>Company, country</th>
<th>Type of formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madopar</td>
<td>Levodopa(100 mg) Benserazide(25mg)</td>
<td>Roche product, USA</td>
<td>Floating CR capsule</td>
</tr>
<tr>
<td>Valrelease</td>
<td>Diazepam(15mg)</td>
<td>Hoffmann- LaRoche, USA</td>
<td>Floating capsule</td>
</tr>
<tr>
<td>Liquid gaviscon</td>
<td>Al(OH)₂(95mg) MgCarbonate(385mg)</td>
<td>GSK, India</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
<tr>
<td>cytotec</td>
<td>Misoprostal(100µgm/200 µgm)</td>
<td>Pharmaacia,USA</td>
<td>Bilayer floating capsule</td>
</tr>
<tr>
<td>Topalkan</td>
<td>Aluminum magnesium antacid</td>
<td>Pierre Fabre drug, France</td>
<td>Floating liquid alginate</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulfate</td>
<td>Ranbaxy, India</td>
<td>Gas generating floating form</td>
</tr>
<tr>
<td>Cifran OD</td>
<td>Ciprofloxacin(1gm)</td>
<td>Ranbaxy, India</td>
<td>Gas generating floating form</td>
</tr>
</tbody>
</table>
1.9. Polymers Used in Floating Drug Delivery Systems

Following types of ingredients can be used to prepare FDDS in addition to the drugs:

- **Hydrocolloids (20%-75%):** They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. Eg. Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, HPC etc.

- **Inert fatty materials (5%-75%):** Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Eg. Beeswax, Sunflower oil, Soybean oil, Fatty acids, Long chain fatty alcohols, Gelucires® 39/01 and 43/01.

- **Effervescent agents:** Sodium bicarbonate, Citric acid, Tartaric acid, Di-Sodium Glycine Carbonate, Citroglycine etc.

- **Release rate accelerants (5%-60%):** eg Lactose, Mannitol

- **Release rate retardants (5%-60%):** eg Dicalcium phosphate, Talc, Magnesium stearate

- **Buoyancy increasing agents (upto80%):** eg. Ethyl cellulose

- **Low density material:** Polypropylene foam powder (Accurel MP 1000®).

1.10. Classification of Floating Drug Delivery Systems

Based on the formulation variables FDDS are classified into effervescent and non-effervescent systems.

**A. Effervescent Floating Drug Delivery Systems:**

These buoyant systems utilize matrices prepared with swellable polymers like Methocel®, Chitosan and various effervescent compounds like sodium bicarbonate, tartaric acid and citric
acid. They are formulated in such-a-way that when in contact with the acidic gastric contents, carbon dioxide is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms (Fig. 1.6).

![Fig. 1.6. (A) Multiple unit oral FDDS, (B) Working principle of effervescent FDDS.](image)

**B. Non-effervescent Floating Drug Delivery System:**

Non-effervescent floating drug delivery system use a gel forms or swellable cellulose type of hydrocolloids, polysaccharides and matrix forming polymers like polycarbonate, polyacrylate, polymethacrylate and polystyrene. Here floating property is achieved by following two mechanisms:

- The dosage form swells when it comes in contact with gastric fluids and attains a bulk density less than 1, the air entrapped within the swollen matrix imparts buoyancy to the dosage form. The soformed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. Ex: Floating tablet.

- The inherent low density of dosage form helps in the buoyancy of the dosage form. Ex: Microporous compartment system.

This system can be further divided into four sub types:
I. Microporous Compartment System:

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

II. Colloidal Gel Barrier System:

This system incorporates a high level of one or more gel forming cellulose type hydrocolloid e.g. hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system swells and forms a colloid gel barrier around its surface maintaining its shape (Fig. 1.7). The air trapped by the swollen polymer confers the buoyancy of the dosage form and a bulk density less than unity. The gel barrier controls the rate of diffusion of solvent - in and drug out of the dosage form. They are formulated as tablet or capsule.
Fig. 1.7. Working principle of hydro dynamically balanced system.

III. Alginate Beads:

Multi-unit floating spherical floating beads of approximately 1.5 mm to 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride. Spherical gel beads formed instantaneously due to intermolecular cross linking between the divalent calcium ions and the negatively charged carboxyl group of alginic acid provided a gel barrier at the surface of the formulation. The beads are then separated, dried at 40ºC. These beads when administered absorb gastro intestinal fluid and swell decreasing it’s density and hence get floated (Fig. 1.8).

Fig. 1.8. Figure showing floating of alginate beads.
IV. Hollow Microspheres/ Microballons:

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method [30]. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane forming an internal cavity in the microsphere of the polymer with drug (Fig. 1.9). The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h.

![Fig 1.9. Figure showing mechanism of formation of microballoon.](image)

1.11. Mechanism of Drug Release from Beads

The mechanism of drug release from beads can be occurring in the following ways:

a) **Diffusion:** On contact with aqueous fluids in the GIT, water diffuses into the interior of the bead. Drug dissolution occurs and the drug solutions diffuse across the gel barrier to the exterior.
b) **Erosion:** Some coating can be designed to erode gradually with time, thereby releasing the drug contained within the bead.

c) **Osmosis:** In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the bead. The drug is forced out of the bead into the exterior through the coating.

### 1.12. Literature Review

**Floating Tablets:**

Pandit et al [31] prepared gastro retentive floating tablets of amoxicillin trihydrate using various grades of HPMC with the objective to obtain site-specific drug delivery and to extend its duration of action. Optimized formulation of amoxicillin was found to have increased gastric residence prolonging the release of drug with 85% of drug release in 6 h by diffusion. The mechanism of drug release was found to be diffusion and followed combination of zero order and first order kinetics.

Yin et al [32] developed gastro-floating tablets of cephalexin to prolong the residence time in major absorption sites. Gastro-floating tablets were prepared and optimized using hydroxypropyl methylcellulose (HPMC K100M) as matrix and sodium bicarbonate as a gas-forming agent. The properties of the tablets in terms of floating lag time, floating time and in-vitro release were evaluated. Furthermore, in-vivo pharmacokinetic study in fed and fasted beagle dogs was performed. The gastro-floating tablets had short floating lag time and exhibited a satisfactory sustained-release profile in-vitro. Compared with conventional capsules, the gastro-floating tablets presented a sustained-release behavior with a relative bioavailability of 99.4%, while the reference sustained-release tablets gave a relative bioavailability of only 39.3%. Meanwhile, the
food had significant effect on the pharmacokinetics of sustained-release tablets. It was concluded that the gastro-floating tablets had a sustained-release effect in-vitro and in-vivo, as well as desired pharmacokinetic properties in both fed and fasted conditions.

Arza et al [33] developed swellable, floating, and sustained release tablets of ciprofloxacin by using a combination of hydrophilic polymer (hydroxypropyl methylcellulose), swelling agents (crospovidone, sodium starch glycolate, and croscarmelose sodium) and effervescent substance (sodium bicarbonate). Formulations are evaluated for percentage swelling, in-vitro drug release, floating lag time, total duration of floating, and mean residence time (MRT) in the stomach. In-vivo nature of the tablet at different time intervals is observed in the radiographic pictures of the healthy volunteers and MRT in the stomach is found to be 320±48.99 min (n=6). A combination of HPMC K100M, crospovidone, and sodium carbonate shows the good swelling, drug release, and floating characters than the marketed CIFRAN OD®.

Patel et al [34] designed floating matrix tablets of clarithromycin to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Floating tablets of clarithromycin containing HPMC and different additives were compressed using wet granulation and D-optimal design technique. The study shows that tablet composition and mechanical strength have great influence on the floating properties and drug release. Incorporation of gas-generating agent together with polymer improved drug release, besides optimal floating (floating lag time <30 s; total floating time >10 h). The drug release was sufficiently sustained (more than 8 h) and anomalous diffusion as well as zero-order was confirmed. The optimized formulation was obtained using 62.5% clarithromycin, 4.95% HPMC
K15M, 18.09% HPMC K4M, 12.96% sodium bicarbonate which gave floating lag time < 30 s with a total floating time > 10 h.

Bomma et al [35] developed floating matrix tablets of norfloxacin to prolong gastric residence time, leading to an increase in drug bioavailability. Tablets were prepared by the wet granulation technique, using polymers such as HPMC (HPMC K4M, HPMC K100M) and xanthan gum. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium. In-vivo radiographic studies revealed that the tablets remained in the stomach for 180 ± 30 min in fasting human volunteers and indicated that gastric retention time was increased by the floating principle, which was considered desirable for the absorption window drugs.

Chavanpatil et al [36] Developed a new gastroretentive sustained release delivery system with floating, swellable and bioadhesive properties for ofloxacin using various release retarding polymers like psyllium husk, HPMC K100M and a swelling agent, crosspovidone. Formulations were evaluated for in-vitro drug release profile, swelling characteristics and in-vitro bioadhesion property. The in-vitro drug release followed Higuchi kinetics and the drug release mechanism was found to be of anomalous or non-Fickian type. The similarity factor f2 was found to be 91.12 for the developed formulation indicating the release was similar to that of the marketed formulation (Zanocin OD). The swelling properties were increased with increasing crosspovidone concentration and contributed significantly in drug release from the tablet matrix. The bioadhesive property of the developed formulation was found to be significant (P < 0.005) in combination as compared to HPMC K100M and psyllium husk alone.

Yang et al [37] proposed a new strategy for the triple drug treatment (tetracycline, metronidazole and bismuth salt) of H. pylori associated peptic ulcers. The design of the delivery system was
based on the swellable asymmetric triple layer tablet approach, with floating feature in order to prolong the gastric retention time of the delivery system. Hydroxypropyl methylcellulose and poly (ethylene oxide) were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt could be included in one of the outer layers for instant release. Results demonstrated that sustained delivery of tetracycline and metronidazole over 6–8 h can be easily achieved while the tablet remained afloat. The floating aspect was envisaged to extend the gastric retention time of the designed system to maintain effective localized concentration of tetracycline and metronidazole. Authors concluded that the developed delivery system has potential to increase the efficacy of the therapy and improve patient compliance.

**Floating Capsules:**

A new peroral amoxicillin/clavulanate therapeutic system composed of immediate release tablet and controlled release floating capsule was developed and evaluated by in-vivo bioavailability study by Kerč and Opara [38]. Pharmacokinetic (PK) parameters for amoxicillin and clavulanic acid of the new therapeutic systems: AUCt, AUCi, (AUCt/AUCi), Cmax, Tmax, kel, T1/2 and additionally for amoxicillin T4 and T2 were calculated from the plasma levels. The study confirmed enhanced pharmacokinetic parameters of a newly developed therapeutic system containing 1500 mg of amoxicillin and 125 mg of clavulanic acid. Prolonged time over MIC(minimum inhibitory concentration) of amoxicillin in relation to a regular immediate release amoxicillin/clavulanate formulation was also confirmed.

Neb et al [39] developed hydrodynamically balanced capsules of clarithromycin to prolong gastric residence time with the desired in-vitro release profile for the localized action in the
stomach, in the treatment of *H. pylori* mediated peptic ulcer. HPMC K4M and Carbopol 934 were selected as release modifier polymeric fillers and sodium bicarbonate as the float accelerator. The capsules were prepared by physical blending of clarithromycin and the polymer in varying ratios. Incorporation of gasgenerating agent together with polymer improved drug release, besides optimal floating. A $3^2$ factorial design was applied to study the effect of individual formulation variables on the final formulation and their interaction with each other. The formulation developed using 30% HPMC K4M polymer and 10% sodium bicarbonate showed promising responses with respect to n, t50, t85 and Q12.

**Floating Beads:**

Sahasathian et al [40] formulated chitosan-coated mucoadhesive floating alginate beads as a gastroretentive delivery vehicle for amoxicillin, towards the effective eradication of *H. pylori*, a major causative agent of peptic ulcers. Amoxicillin loaded alginate beads coated with 0.5% (w/v) chitosan exhibited excellent floating ability, high encapsulation efficiency, high drug loading capacity, sustained release of amoxicillin for over six hours in simulated gastric fluid and a strong in-vitro mucoadhesion to the gastric mucosal layer. Fursule et al [41] described the formulation and evaluation of gastroretentive system of an antibacterial agent, amoxicillin trihydrate, based on the concept of altered density. Different formulations of oil entrapped floating gel beads were prepared by using sodium alginate as gelling agent. The prepared beads were evaluated for diameter, surface morphology and encapsulation efficiency. Authors concluded that the oil entrapped gel beads can be used as FDDS for local as well as systemic drug delivery.
Nimase et al [42] prepared multiple-unit floating beads of clarithromycin containing sodium alginate hydroxypropyl methylcellulose (K100M) and sunflower oil using the technique of three variables at three levels ($3^3$) factorial design. Total twenty-seven possible batches were prepared and were evaluated for entrapment efficiency, drug loading, buoyancy and in-vitro drug release. All formulations showed floating lag time below 2 minutes and showed total floating duration more than 10 h. The release rate, entrapment efficiency, drug loading and buoyancy was greater with formulation containing 2 percent sodium alginate solution and 5 percent calcium chloride solution along with 5 ml sunflower oil.

Gattani et al [43] developed alginate/HPMC based floating-mucoadhesive beads of clarithromycin to provide prolonged contact time of antibiotic to treat stomach ulcer. Beads were prepared by ionic gelation technique where calcium chloride used as gelating agent and incorporated liquid paraffin for floating of the beads. Prepared beads were evaluated extensively for particle size, drug entrapment; swelling and surface morphology by using scanning electron microscopy. X-ray radioimaging study in rabbits, in-vitro mucoadhesion using rat stomach mucosal membrane and in-vitro drug release studies were carried out. Ex-vivo performance of alginate-HPMC beads were studied using albino rats in comparison to simple alginate-calcium beads. Authors concluded that alginate-HPMC beads may be suitable floating-muco-adhesive drug delivery system for delivering clarithromycin to treat stomach ulcers.

Srinatha et al [44] prepared chitosan beads loaded with ciprofloxacin hydrochloride and fabricated by ionic cross-linking with sodium tripolyphosphate. Authors found that minimum curing time is important for high drug loading. Authors also found that drug release increased with higher concentration of drug in decreasing proportion of chitosan.
Floating Granules:
Shah et al [45] prepared controlled-release multiunit floating lipid granules of gatifloxacin using Gelucire 39/01, and Gelucire 43/01 by the melt granulation technique and evaluated for in-vitro floating and drug release. Ethyl cellulose was taken as release rate modifier. Authors found that moderate amount of Gelucire 39/01 and ethyl cellulose provides desired release of gatifloxacin from a floating system. The temperature sensitivity studies for the prepared formulations at 40˚C/75% relative humidity for 3 months showed no significant change in in-vitro drug release pattern.

Floating Micro Particles:
Patel et al [46] prepared mucoadhesive amoxicillin microspheres by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent and chitosan as mucoadhesive polymer. In-vitro mucoadhesive test showed that amoxicillin mucoadhesive microspheres adhered more strongly to gastric mucous layer and could retain in gastrointestinal tract for an extended period of time. The best batch exhibited a high drug entrapment efficiency of 70% and a swelling index of 1.39; percentage mucoadhesion after 1 h was 79 %. The drug release was also sustained for more than 12 h. Results of in-vivo H. pylori clearance tests on Wistar rats showed that amoxicillin mucoadhesive microspheres had a better clearance effect than amoxicillin powder. Authors concluded that the prolonged gastrointestinal residence time and enhanced amoxicillin stability resulting from the mucoadhesive microspheres of amoxicillin might make contribution complete eradication of H. pylori.

Cuna et al [47] prepared microparticles of amoxicillin-loaded ion-exchange resin encapsulated in polycarbophil and Carbopol 934 mucoadhesive polymers by modified oil-in-oil solvent
evaporation technique. The prepared microspheres were evaluated for morphology and size, drug release, drug content and gastric transit time in rats. Polycarbophil microparticles were spherical, while carbopol 934 microparticles were irregular. In-vitro release of amoxicillin was rapid with or without a polymer coating. However, the gastrointestinal transit time was longer, and the distribution of the particles on the mucosa apparently better, without any polymer coating. Therefore, the authors concluded that microencapsulation of ion-exchange resin particles in the mucoadhesive polymers polycarbophil and Carbopol 934 failed to prolong their residence in the stomach of rats to a significant extent and appeared to favour the aggregation of the particles thereby making the distribution of particles in the stomach more difficult.

Nagahara et al [48] formulated amoxicillin in the form of mucoadhesive microspheres by spray chilling method, which have the ability to reside in the gastrointestinal tract for an extended period. The microspheres contained the amoxicillin and carboxyvinyl and curdlan as adhesive polymers dispersed in melted hydrogenated castor oil. The prepared microspheres were compared to 0.5% methylcellulose amoxicillin suspension in infected Mongolian gerbils under feeding conditions. The percentage of amoxicillin remaining in the stomach both 2 and 4 h after oral administration of the mucoadhesive microspheres was about three times higher than that after administration in the form of a 0.5% methylcellulose suspension. Both formulations showed anti *H. pylori* effects, with effective reduction of the required dose of amoxicillin by a factor of 10 when the mucoadhesive microspheres were used.

Karthikeyan et al [49] studied effect of different grades of HPMC on cefpodoxime proxetil release profile from floating microspheres. The cefpodoxime proxetil microspheres were prepared by non aqueous solvent evaporation method using HPMC K15M(15cps), HPMC4M(4000cps), HPMC100LV(100cps) and ethyl cellulose. The prepared floating
microspheres were found to produce the percentage yield of 50.5-72.21%, drug entrapment efficiency of 14.1-28.2%, buoyancy percentage of 70.1-88.25% and drug release of 65.09-101.88%. The better drug release profile was found to be formulation with drug : polymer ratio of 1:2 and HPMC 15cps showed much significant increase in the drug release while comparing with the other two grades of HPMC.

Deepa et al [50] prepared floating microspheres of cefpodoxime proxetil in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. The microspheres were prepared by non-aqueous solvent evaporation method using polymers such as HPMC K15M, ethyl cellulose in different ratios and cefpodoxime proxetil in each formulation. The yield, particle size, buoyancy percentage, drug entrapment efficiency, and in-vitro drug release were studied. The result showed that microspheres yielded 50.5-72.2%, particle size was 75-600 μm, drug entrapment efficiency was 14.1-28.2%, and buoyancy percentage was 70.1-88.3%. The best drug release profiles were seen with formulation having the ratio of drug to polymer of 1:2.

Sarojini et al [51] developed albumin-chitosan based floating mucoadhesive microsphere of clarithromycin to provide prolonged contact time for drug delivery of antibiotics to treat stomach ulcers, increase the gastric residence time, decrease the diffusional distance, and also act locally at the infectious site. Microspheres prepared by heat stabilization method in the presence of span-80 were optimized by varying different formulation and processes parameters like drug to polymer ratio. It was subjected to evaluation for particle size, incorporation efficiency, in-vitro buoyancy and in-vitro drug release. Drug release from microsphere was found to be first order. It was concluded that drug-loaded microsphere appear to be a suitable delivery system for clarithromycin.
Venkateswaramurthy et al [52] developed controlled release mucoadhesive microspheres of amoxicillin trihydrate for the treatment of peptic ulcer disease caused by *H. pylori*. Microspheres were prepared by solvent evaporation technique using carbopol 974P, hydroxypropyl methyl cellulose K4M (HPMC K4M) and Eudragit RS 100 and were subjected to evaluation for particle size, incorporation efficiency, in-vitro mucoadhesion and in-vitro drug release characteristics. The prepared microspheres showed a strong mucoadhesive property. The polymer concentration influenced the in-vitro drug release significantly in 0.1N HCl. The particle sizes of systems ranged between 123±8.35 μm and 524±11.54 μm. The percentage drug entrapment and percentage yield of formulations were about 56.71±1.66% to 88.32±0.65% and 39.20±1.62% to 92.40±1.32%, respectively. The stability of the drugs was assessed in 0.1 N HCl. The results further substantiated that mucoadhesive microspheres improved the gastric stability of amoxicillin trihydrate (due to entrapment within the microsphere).

Sahoo et al [53] developed floating microspheres of ciprofloxacin hydrochloride by simple dripping method using a polymer mixture of sodium alginate and hydroxyl propyl methyl cellulose and sodium bicarbonate as gas forming agent. The prepared floating microspheres were evaluated for particle size distribution, floating behavior, drug content and in-vitro drug release. The prepared microspheres showed enhanced buoyancy and controlled release of the drug.

**Floating Nanoparticles:**

A novel hydrogel nanoparticles containing amoxicillin were synthesized by Moogooee et al [54]. The drug loaded hydrogel nanoparticles were prepared using the mucoadhesive polymer cross-linked N-isopropylacrylamide-acrylic acid-hydroxyethyl methacrylate. The prepared nanoparticles were characterized for their entrapment efficiency, mean diameter, morphology
and in-vitro release in both pH 1.0 and 7.4 media. It was found that about 88.5% of amoxicillin entrapped in the nanoparticles was released in 4 h in the pH 1.0 medium, whereas in phosphate buffer at pH 7.4 not more than 45% was released after 4 h of dissolution study. In-vivo studies were performed to determine the drug concentration in rats' gastric tissues. The studies revealed that the hydrogel nanoparticles enhance drug concentration at gastric site than powder amoxicillin. Thus, the authors concluded that the developed hydrogel nanoparticle formulation may provide therapeutic concentration at a much lower dose that may reduce the adverse effects of amoxicillin in high doses.

**In-Situ Floating Gels:**

Mishra et al [55] prepared floating in situ gelling system of clarithromycin (FIGC) using gellan as gelling polymer and calcium carbonate as floating agent for potentially treating gastric ulcers, associated with *H. pylori*. Gellan based FIGC was prepared by dissolving varying concentrations of gellan in deionized water to which varying concentrations of drug and sucralfate were dispersed well. The formulation parameters like concentrations of gellan gum and sucralfate influenced the rate and extent of in-vitro drug release significantly from FIGC. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low pH. The in-vivo *H. pylori* clearance efficacy of prepared FIGC and clarithromycin suspension following oral administration, to *H. pylori* infected Mongolian gerbils was examined by polymerase chain reaction (PCR) technique and by a microbial culture method. FIGC showed a significant anti-*H. pylori* effect than that of clarithromycin suspension. The in situ gel formulation with sucralfate cleared *H. pylori* more effectively than that of formulation without sucralfate. In addition, the required amount of clarithromycin for eradication of *H. pylori* was
found to be less from FIGC than from the corresponding clarithromycin suspension. It was concluded that prolonged gastrointestinal residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin might contribute better for complete clearance of *H. pylori*.

A gellan based floating in situ gelling system for controlled delivery of amoxicillin was developed by Rajinikanth et al [56]. The systems were prepared by dissolving varying concentrations of gellan gum in deionized water containing sodium citrate, to which varying concentrations of drug and calcium carbonate, as gas-forming agent, was added and dissolved by stirring. The in-vivo *H. pylori* clearance efficacy of prepared amoxicillin floating in situ gelling system (AFIG) was studied in *H. pylori* infected Mongolian gerbils following repeated oral administration by polymerase chain reaction technique and by a microbial culture method in comparison to amoxicillin suspension. The AFIG showed a significant anti-*H. pylori*, where the required amount of amoxicillin for eradication of *H. pylori* was 10 times less than that from the corresponding amoxicillin suspension.

### 1.13. Conclusion

FDDS is a novel drug delivery system which is so far limited to the experimental works, but system is having lot of prospective. In present era, therapeutic efficacy is a major issue in front of formulation and development pharmacists. In such situation FDDS will play an important role. FDDS reduces the fluctuations in the plasma level of antimicrobials delaying their gastric emptying. Antimicrobials that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract or low bioavailability due to extensive first pass metabolism or have a
local action in stomach can be delivered efficiently by FDDS thereby improving their therapeutic efficacy.

1.14. References


